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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,715	02/13/2002	Michael Chopp	1059.00073	9739

7590 10/03/2008

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
10/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/075,715	CHOPP ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/14/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8 and 14-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-8 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/14/08 has been entered.

The response filed 7/14/08 presents remarks and arguments to the office action mailed **3/17/08**. Applicant's request for reconsideration of the rejection of claims in the last office action has been considered.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Declaration

The Declaration filed on 7/14/08 under 37 CFR 1.131 is sufficient to overcome the 112 first paragraph written description because Applicant has shown that all PDE inhibitors increase cGMP and not only PDE5.

Status of claims

Claims 1, 6-8 and 14-17 are pending in this application.

Withdrawn *Claim Rejections - 35 USC § 112*

Claims 1, 6-8 and 14-17 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This written description rejection is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6-8, 14-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear what is meant by "administering a post ischemic event" to a patient in the above claims. What is meant by "administering a post ischemic event"? Is there such an administration?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6-8 and 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Endres et al., Pro. Natl, Aca. Sci, 95; pp 8880-8885, 1998.

Endres et al disclose administering statins to patients for the treatment of ischemia. The reference further discloses that HMG-CoA (3-hydroxy-3-methylglutaryl–coenzyme A) can reduce cerebral ischemia by up regulating eNOS (endothelial nitric oxide synthase) expression. See abstract and entire page 8880 and also discussion.

As to the mechanistic function affecting new neuron growth, increasing levels of cGMP; augmenting, increase neurological function will inherently occur once the drug is administered regardless of the condition being treated. It is noted that all patients would be expected to be within the patient population who have been given or administered the statin drug. Neurogenesis is a process of regenerating new neurons, or extension of the old neurons. Thus, anyone or any patient population taking the drug for whatever disease condition, the mechanistic function of the drug will be the same i.e., increase neurons, increase cGMP, and increase in cognitive and neurological functions. Thus anyone taking the drug will affect neurogenesis. Further the claims recite administering to a patient "in need thereof". While the function is mechanistic in nature, it is not

limiting in this instance, because everyone needs neurogenesis as they age and in need thereof is inclusive to anyone in need of neurogenesis.

Claim Rejections - 35 USC § 102 (is reinstated) after careful consideration

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 6-8 and 14-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Liao, US 6,423,751.

Liao teaches up regulation of endothelial cell nitric oxide synthase expression (column 3, lines 24-31) by administration of HMG CoA reductase inhibitors such as atorvastatin for the treatment of post stroke (see col. 9, lines 20-30, column 15, line 38 to column 16, line 12). Liao teaches that a surprising connection was made in connection with the treatment of ischemic stroke wherein brain injury reduction is measured by determining a reduction in the infarct size in the treated versus the control groups. Cerebral blood flow was better in the treated animals and it is believed that the

positive results are attributable 1o the up regulation of endothelial cell nitric oxide synthase activity (column 8, line 59 to column 9, line 8).

Augmenting, production of neurons, increasing neurological function and cognitive function are viewed as the mechanistic function. Functions such as affecting new neuron growth, increasing levels of cGMP; augmenting, increase neurological function will inherently occur once the drug is administered regardless of the condition being treated. Also note that anyone taking the drug will have the affect of neurogenesis. It is noted that all patients would be expected to be within the patient population who have been given or administered the statin drug. The same function must inherently occur when the same drug is administered. Neurogenesis is a process of regenerating new neurons, or extension of the old neurons. Thus, anyone or any patient population taking the drug for whatever the disease condition, the mechanistic function of the drug will be the same i.e., increase neurons, increase cGMP, and increase in cognitive and neurological functions. Thus anyone taking the drug will affect neurogenesis. Further the claims recite administering to a patient "in need thereof". While the function is mechanistic in nature, it is not limiting in this instance, because everyone needs neurogenesis as they age and in need thereof is inclusive to anyone in need of neurogenesis.

Maintained Claim Rejections - 35 USC § 103

Claim 1 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Quast et al., Brain research 677(20 1995, 204-212 taken with Horackova et al. Am. J. Physiol. Cell 269(2) Abstract only, 1995 in view of Cooke et al. US 5,428,070.

Applicant argues that Quast has nothing to do with neurogenesis and recovery of function especially by administering a NO donor that Quast et al show that the presence of NO is detrimental to ischemic brain injury, while the instant application shows NO donors which increase NO and cGMP improve neurological function.

Next Applicant argues that Harackova et al, showed *in vitro* investigation and not *in vivo* and that the reference has nothing to do with the claimed invention, that the Harackova reference was incorrectly applied.

With regards to the Cooke et al reference, Applicant argues that the patent explicitly addresses the role of administering L-arginine as a substrate for nitric oxide in the treatment of atherosclerosis and restenosis. Applicant further argues that with regards to COOKE there is no reference to brain, neurogenesis, recovery from stroke, and that the reference is directed to reduction of vascular pathology associated with atherosclerosis.

In response, the Quast reference teaches that nitric oxide synthase inhibitor nitro-L-arginine methyl ester decreases ischemic damage in reversible focal cerebral ischemia. Applicant cited the conclusionary statement on page 211 referring that the presence of (NO) is detrimental to ischemic brain damage.

This is found not persuasive because the reference clearly states that by oxide inhibiting nitric oxide radical ($NO^{\cdot}$) plays an important role/mediating in hyperglycemia-exacerbated ischemic brain injury and by inhibiting the nitric oxide radical the low dose of L-NAME dramatically attenuates injury to the brain cells eliminating the formation of a large no reflow zone. See page 211 last paragraph.

It is quiet clear that ischemic is a condition in which blood flow is restricted once the L-NAME is administered. See also abstract line 8. As to the argument that the reference does not teach the increase level of cGMP and affecting new neuron growth, it is the understanding that once the product is administered, it is expected to function as claimed. L-NAME is an arginine analog administering it is administering L-arginine. Further it is known to one of ordinary skill in the art that nitric oxide (NO) is synthesized from the physiologic precursor L-arginine by the stereospecific enzyme NO synthase. And NO causes relaxation of the smooth muscle by activating soluble guanylate cyclase to increase cyclic GMP. Since the level of cGMP is increased one of ordinary skill in the art would assume that the neurons are also increased. Thus there properties cannot be separated from the compound.

With regard to the Horackova et al. argument supra, Applicant should note that this is not a 102 rejection, and this reference was introduced for the showing that nitric oxide synthesizing neurons are present after the administration of a nitric oxide donor S—nitroso-N-acetylpenicillinamine implying new neurons are made. See underlining abstract and page C505 underlined sec. As to the allegation that the reference only teaches in vitro analysis is found not persuasive because the cells

employed in the reference are from the mammal's heart. It is also common practice to investigate through cells, then further into preclinical trials where mammals (animals) are employed before taking the research further to various stages of clinical trials based on the success. So far from cursory review of the literature it is noted that L-arginine has been taken into clinical trial and now has been adapted as a form of treatment, therefore the showing that neurons are increased by Horackova, ties in with the above reference showing the increase in neuron generating when L-arginine is administered. See page C506, where in the reference specifically teach administration of L-arginine increase the cardiac neurons. Underlined section.

As to the argument that Cooke does not teach the claimed invention is noted, but Applicant should again be aware that this is a 103 rejection that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Clearly, Cooke reference teaches post stroke, when the drug L-arginine is administered after the injury (post). It is the Examiners interpretation that after injury is considered post, unless otherwise it clearly teaches the post stroke limitation. See col. 3, lines 52-55 as cGMP is increased (see col. 9, lines 22-24) thus, will result in new neuron growth as already discussed above. Thus as stated in the last office action of record one of ordinary skill in the art would have been motivated to administer L-arginine to patients

post stroke in order to promote neurogenesis, or growth of new neurons, because *L*-arginine is the substrate for nitric oxide (NO) production and has been shown to induce an endothelium-dependent increase in cerebral blood flow in humans. And as shown, increase in cGMP was achieved by administration of L-arginine; see col. 9, lines 22-24 (Cooke).

Applicant's arguments have been fully considered but they are not persuasive. For the above reasoning's and the rejection is maintained as in the last office action of record.

Claims 1 and 6-8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cooke et al., US 5,428,070 taken with Liao, US 6,423,751, in view of Kaposzta, (*Circulation*. 2001;103:2371-2375) taken with Ohtsuka et al., The American J. of Med. Vol. 108, (5) 2000, 439 (of record) further in view of (newly applied) Quast et al., Brain research 677(20 1995, 204-212 taken with Horackova et al. Am. J. Physiol. Cell 269(2) Abstract only, 1995.

Applicant arguments and rebuttal to the Quast, Horakova and Cooke reference is applied here.

As to the Liao reference, Applicant argues that the invention is for treating subjects with hypoxia –induced condition and that there is no reason to interpret the statement "… is useful for treating subjects with hypoxia-induced condition". Further, Applicant argues that a journal article by Liao, provide evidence that Liao only discloses prophylactic treatment or at most during a stroke.

Applicant also alleges that the Ohtsuka and Kaposta references merely disclose the use of the compounds prophylactically. In conclusion Applicant states that none of the references disclose any evidence of production of new neurons.

In response, it is not clear what the Applicant is arguing with regard to Liao, first Applicant states that the Liao reference does not teach the claimed invention, then further states that it only provides evidence that Liao only discloses prophylactic treatment.

As stated in the office action, the Liao reference teaches the use of statins for the treatment of patients who have experienced stroke. Accordingly, have experienced stroke is post stroke. Liao teaches up-regulation of endothelial cell nitric oxide synthase expression (col. 3, lines 24-31) by administration of HMG-Co reductase inhibitors for example atorvastatin, fluvastatin, cerivastatin (all statins) for the treatment of stroke (patients having experience stroke, see col. 9, lines 20-30.
The kaposta reference teaches the administration of L-arginine in combination with S-nitrglutathione (a nitric oxide donor) in the treatment of postoperative stroke risk, see page 2371 of record.
Ohtsuka et al. teach cognitive functions increased with the administration of L-arginine (see report).

From the showing, of the references it is clear that the combined references would have resulted in the claimed invention and as evident by Jeremy et al. British J. Urology 1997, 79, 958-963, a phosphodiesterase inhibitor type 5 such as sildenafil increases cGMP, it is expected to function the same when administered, that is increase

the growth of new neurons. Applicant's arguments have been fully considered but they are not persuasive for the above reasons. The rejection is maintained as in the last office action.

Claims 14-17 rejected under 35 U.S.C. 103(a) as being unpatentable over Liao, US 6,423,751 is withdrawn. Applicant's argument is persuasive. Upon further search new rejections are being made.

Claims1, 6-8 and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jeremy et al. British J. Urology 1997, 79, 958-963 and Poluha et al., J. Biological Chem. 272(38) 24002-24007(already of record) in view of Liao, US 6,423,751.

Jeremy et al teach that sildenafil increases cGMP and also may enhance erection by augmentation of nitric oxide mediated relaxation pathway, see conclusion, thus affecting new neuron growth in a patient and augmenting the production of neurons as required by instant claims 1, 6-8, 14-15. The reference fails to teach explicitly increased cognitive and neurological functions.

Poluha teaches a nitric oxide donor to be a nerve growth factor NGF) (see abstract), of neuron growth, (pp 24006 end of 1st paragraph), augmenting to (a site in need of see fig 1.). Poluha also teaches increase levels of cGMP (see page 24005 last paragraph) using NGF. Poluha teaches that treating PC12 cell with the nerve growth factor leads to production of nitric oxide (abstract and entire paper) and nitric oxide results in an increase in cGMP (ref, P 24005, left column. The Poluha et al. reference

also teaches (p 24005, left column) that it also results is neutrite extension, i.e. per understanding effecting neurogenesis.

Liao teaches up-regulation of endothelial cell nitric oxide synthase expression (col. 3, lines 24-31) by administration of HMG-Co reductase inhibitors for example atorvastatin, fluvastatin, cerivastatin (all statins) for the treatment of stroke (patients having experience stroke, see col. 9, lines 20-30. Liao teaches a surprising connection was made in the treatment of ischemic stroke wherein brain injury reduction is measured by determining a reduction in the infarct size in the treated versus the control groups. See col. 8, lines 59-65.

Although all of the above references do not teach the increased cognitive effect it is assumed that the functions of agents such as those in the Liao reference will have the same property as the claimed agents since they are the same agents/compounds/drugs employed, thus will argument, and affect neurogenesis and the growth of new neurons. Secondly as taught by Liao et al. the administrations of these agents resulted in brain injury reduction which directly correlates with increasing neurological functions. Even though increase neurological function was demonstrated in a patient with erectile dysfunction it shows that the drug of Jeremy et al and Liao are capable of increase any neurological functions that involves neurons when administered to a patient in need thereof. Thus from the knowledge of one of ordinary skill in the art that nitric oxide is responsible for neurogenesis, meaningly neurogenesis support new growth or augment to old to proliferate as discussed in the Poluha et al reference.

Therefore one of ordinary skill in the art would be motivated to increase nitric oxide either by administering a nitric oxide donor directly or administering drugs such as sildenafil because these drugs are known in the art to increase cGMP and increase neurological function.

Also, with regards to increasing neurological function and cognitive in a patient as stated by MPEP it is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that the subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second first full para.).

Maintained Double Patenting

The provisional obviousness type double patenting rejection is not the only rejection in the examined application and the rejection will continue to be made until the rejection is overcome as stated in MPEP 804 [R-5], I B, that "the "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications." As noted above, the provisional obviousness double patenting rejection is not the only rejection remaining in this examined application. Thus rejection is maintained and is not held in abeyance.

Claim **1, 6 – 8 and 14-17** remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-13** of U.S. Patent Application No. **10,500,694**. Although the conflicting claims are not identical, they are not patentably distinct from each other.

No claim is allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, Art Unit 1618 October 3, 2008